Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa

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Abstract

Objectives

To determine retention in HIV care for individuals not yet eligible for antiretroviral therapy (ART) and to explore factors associated with retention in a rural public health HIV programme.

Methods

HIV-infected adults (≥16 years) not yet eligible for ART, with CD4 cell count >200cells/μl January 2007 - December 2007 were included in the analysis. Retention was defined by repeat CD4 count within 13 months. Factors associated with retention were assessed using logistic regression with clustering at clinic level.

Results

4,223 were included in the analysis (83.9% female). Overall retention was 44.9% with median time to return 201 days (interquartile range [IQR] 127-274). Retention by initial CD4 count 201-350, 351-500, and >500 cells/μl was 51.6% (95% confidence interval [CI] 49.1-54.0), 43.2% (95% CI 40.5-45.9), and 34.9% (95% CI 32.4-37.4) respectively. Compared to CD4 201-350 cells/μl, higher initial CD4 count was significantly associated with lower odds of retention (CD4 351-500 cells/μl adjusted odds ratio [aOR] 0.72, 95% CI 0.62-0.84; CD4 >500 cells/μl aOR 0.51, 95% CI 0.44-0.60). Male sex was independently associated with lower odds (aOR 0.80, 95% CI 0.67-0.96), and older age with higher odds of retention (for each additional year of age aOR 1.03, 95% CI 1.03-1.04).

Conclusions

Retention in HIV care prior to eligibility for ART is poor, particularly for younger individuals and those at an earlier stage of infection. Further work to optimise and evaluate care and monitoring strategies is required to realise the full benefits of the rapid expansion of HIV programmes in sub-Saharan Africa.

Key words: **HIV care; retention; CD4 monitoring; South Africa**

Introduction

South Africa is home to an estimated 5.7 million HIV infected people, approximately one in six of the global HIV infected population[1]. Since 2004, South Africa has seen the scale-up of the largest public sector antiretroviral therapy (ART) programme in the world, yet the number of new HIV infections per year is still considerably more than the number initiated on ART[2]. The scale-up of HIV counselling and testing services has led to increased population testing rates[3-5]. A considerable proportion of newly diagnosed individuals are not yet eligible for ART; in one study from Cape Town between 2001 and 2006 approximately 64% had CD4 cell count measurements above the threshold for eligibility at the time of diagnosis[4]. People living with HIV (PLHIV) who are not yet eligible for ART have received little attention as, in the early phase of antiretroviral roll-out, the priority for HIV services and funding agencies has been on identifying and treating individuals in need of ART[6].

Current WHO guidelines recommend clinical assessment and CD4 count monitoring every 6 months, to determine eligibility for ART as early as possible, and to prevent and treat HIV-related illnesses[7]. Establishing ART eligibility in a timely fashion for individuals enrolled in care is important to reduce the early mortality on ART consistently reported from programmes in sub-Saharan Africa (SSA)[8-13]. Retention in HIV care is also critical to facilitate integration of prevention strategies[14-16].

Despite the recognised importance of retention, there are precious few data from SSA on retention in pre-ART care. In particular, there have been no published studies which explore factors determining pre-ART retention, and hence it remains unclear which groups might benefit most from any targeted supportive intervention. Here we study factors associated with pre-ART retention in a large, decentralised HIV programme, linked to a population demographic platform in rural South Africa.

Methods

Hlabisa HIV Treatment and Care Programme

Hlabisa health sub-district is situated in northern KwaZulu-Natal, South Africa, covering an area of 1430km^2, with approximately 228,000 individuals living largely in scattered homesteads in rural areas. The Hlabisa HIV Treatment and Care Programme is a Department of Health initiative supported by the Africa Centre for Health and Population Studies (www.africacentre.com); details of the programme have been reported previously[13,17]. National ART guidelines are followed which during the study period denoted ART eligibility in the presence of a WHO stage IV condition or CD4 cell count ≤200 cells/μl[18].

All clinics perform CD4 cell count testing and tests are routinely done on the same day for any individual newly diagnosed with HIV infection. CD4 cell counts are performed at the National Health Laboratory Service (NHLS) laboratory at Hlabisa Hospital, using the Beckman Coulter EPICS ® XL flow cytometer (Beckman Coulter, Inc.), and patients are requested to return to clinic for results two weeks from the date of sample collection. Decisions about ART eligibility are usually made on the basis of a single CD4 count result, rarely confirmed in a repeat sample.

The model of care at the time of study for individuals not yet eligible for ART included individual counselling, with advice on healthy living, disclosure, partner notification and testing, transmission risk reduction measures, and family planning. All HIV-infected people regardless of disease stage were additionally invited to attend peer support groups at each clinic. Co-trimoxazole was indicated for individuals with CD4 count ≤200 cells/μl or WHO stage III/IV. Isoniazid preventive therapy (IPT) was not implemented at a programmatic level at the time of study. All individuals were advised to return for repeat clinical assessment, including clinical staging and CD4 count measurement, six months later. Whilst guidelines stipulated repeat CD4 cell count at twelve months if CD4 count >500 cells/μl the actual practice varied and some clinics advised return after six months[19].

For routine programme monitoring and evaluation, all clinic and hospital attendances for CD4 measurement from January 1st 2007 were recorded.

Africa Centre Demographic Information System

A longitudinal demographic surveillance system has, since 2000, collected individual and household demographic data in the demographic surveillance area (DSA), within the Hlabisa health sub-district, which includes approximately 11,000 households and 85,000 individuals[20]. Data are collected 6-monthly on residency status of household members, births, marriages, deaths, and migrations. Data regarding socio-economic status and employment are collected on an annual basis. Data are collated in the Africa Centre Demographic Information System (ACDIS). It is estimated that 30-40% of people in the HIV Treatment and Care Programme are resident in the surveillance area.

Individual records within the HIV Treatment and Care Programme database and ACDIS were linked using the unique South African identity number in accordance with the Africa Centre data confidentiality protocols. Linkage was done to enable analysis of socio-demographic factors associated with retention and to determine vital status of individuals who did not return to care.

Patients

Patients were included in this analysis if they: had a first recorded CD4 cell count from a sample between Jan 1st 2007 – Dec 31st 2007; were ART naive; ≥16 years old at the time of CD4 test; and CD4 count result was >200 cells/μl. Patients were excluded if they: had missing identity number and age/date of birth; and if ART was initiated after the initial CD4 count but before any subsequent CD4 count (it was assumed that these individuals initiated ART on the basis of clinical stage IV disease).

Analysis

Retention was defined as repeat CD4 count within 13 months (395 days) of the initial test; this allowed for visits up to one year from collection of initial test result (as this was the time recommended for those with CD4 count >500 cells/μl). Time to retention was measured using the first

repeat CD4 count within 13 months. CD4 counts within 14 days of the initial test (n = 101) were excluded from the analysis as it was highly likely that the patient had not received the result of the initial test before repeating the test. Further outcome measures were: change in CD4 cell count per month (measured between initial test and first subsequent test); and progression to ART eligibility (CD4 ≤200 cells/μl) within 13 months. End time for all follow-up was Jan 30th 2009.

Additional analyses were performed with individuals linked to the demographic surveillance. Variables were chosen for the analysis either due to reported associations with retention in HIV treatment programmes or postulated effect on retention[21,22]. Residency status related to the defined living arrangements during the course of 13-month follow-up: non-residents were members of households, but not ordinarily resident, within the DSA; in-migrants were initially non-resident but became resident during follow-up; and out-migrants were initially resident but became non-resident. Socioeconomic data were taken from information collected between July and December 2007 (91.6%) or between January and June 2006 (8.4%), whichever was closer in time to the initial CD4 measurement. Household economic status was determined using an asset wealth index[23] and principal component analysis[24]; households were categorized into quintiles according to the wealth index.

Descriptive statistics were used for the baseline characteristics and overall retention. Proportions analysis stratified by age group, sex, and initial CD4 cell count was used to enable full understanding of retention patterns. Logistic regression with clustering at clinic level was used to explore factors associated with retention in care. Multilevel logistic regression models were used to estimate the independence of measured variables (ρ) at clinic level. The effect of missing data was assessed by addition of a "missing" category for each variable in the model and calculation of the log-likelihood p-value. Median regression was used to determine factors associated with CD4 decline. STATA version 10.1 (StataCorp, College Station, Texas) was used for all analyses.

Ethics statement

Ethical approval was obtained from the University of KwaZulu-Natal for the retrospective analysis of anonymised data from the HIV Treatment and Care Programme (BE066/07) and for the linkage of data from the HIV Treatment and Care Programme to the Africa Centre Demographic Information System (E134/06). Approval was also granted by the Research Office of the KwaZulu-Natal Department of Health.

Results

Patients

10,140 individuals had CD4 cell count results recorded between Jan 1st and Dec 31st 2007. 4,223 (41.6%) were eligible for inclusion in the primary analyses and, of those, 930 (22.0%) were matched to ACDIS and were included in the additional analyses (Fig. 1).

3,543 (83.9%) were female. Median age was 31 years (interquartile range [IQR] 25-38) for females and 37 years (IQR 31-45) for males (P<0.001). Median CD4 count was 407 cells/μl (IQR 301-565) for females and 365 cells/μl (IQR 278-491) for males (P<0.001).The distribution across pre-defined CD4 strata was: 1,605 (38.0%) CD4 201-350 cells/μl; 1,278 (30.3%) CD4 351-500 cells/μl; 1,340 (31.7%) CD4 >500 cells/μl.

The individuals matched to ACDIS were similar to the unmatched individuals in terms of sex distribution and initial CD4 cell count, but were marginally older (Table 1). For the matched individuals, the majority remained resident within the demographic surveillance area (DSA) for the 13 month period following the initial CD4 count. Most people (89.4% of those with data) lived within 5km of the nearest primary health care clinic.

Retention in care

Overall 1,896 patients (44.9%) returned for a subsequent CD4 count within 13 months. Of these, 1,371 (72.3%) returned only once and 525 (27.7%) returned on more than one occasion. The proportion retained in care was highest amongst the group with lower initial CD4 cell count: 51.6% for CD4 cell count 201-350 cells/μl (95% confidence interval [CI] 49.1 - 54.0) versus 43.2% (95% CI 40.5 - 45.9) for CD4 cell count 351-500 cells/μl and 34.9% (95% CI 32.4-37.4) for CD4 cell count >500 cells/μl. Retention stratified by age and initial CD4 cell count is illustrated in Fig. 2.

The median time to return was 201 days (IQR 127-274). The time was shortest for the group with lower initial CD4 count: 175 days (IQR 109-251) for CD4 201-350 cells/μl versus 206 days (IQR 153-279) for CD4 351-500 cells/μl and 230 days (IQR 162-310) for CD4 >500 cells/μl (P<0.001).

Change in CD4 cell count and progression to ART eligibility

The median decline in CD4 cell count between initial test and first subsequent test was 8.8 cells/μl per month (IQR -24.9 to +5.16), significantly greater with higher initial CD4 count: -5.2 cells/μl per month for CD4 201-350 cells/μl; -10.5 cells/μl per month for CD4 351-500 cells/μl (P<0.01); and -18.1 cells/μl per month for CD4 >500 cells/μl (P<0.01). In median regression, higher CD4 group and male sex were significantly associated with greater CD4 decline. There was no significant association with age.

516 individuals (27.2% of all those who returned) progressed to CD4 ≤200 cells/μl within 13 months and, of those, 390 (75.6%) were recorded to have subsequently initiated antiretroviral therapy.

Factors associated with retention

In multivariable analysis including all patients, higher initial CD4 count was associated with lower odds of retention (compared to CD4 201-350 cells/μl: adjusted odds ratio [aOR] 0.72 [95% CI 0.62-0.84] for CD4 351-500 cells/μl; and aOR 0.51 [95% CI 0.44-0.60] for CD4 >500 cells/μl). Male sex was independently associated with lower odds of retention (aOR 0.80 [95% CI 0.67-0.96]). With

reference to age 16-25 years, older age was associated with increased likelihood of retention (aOR 1.82 [95% CI 1.55-2.14] for 26-35 years; aOR 2.72 [95% CI 2.25-3.28] for 36-45 years; aOR 3.07 [95% CI 2.43-3.89] for 46-55 years; and aOR 1.89 [95% CI 1.27-2.82] for >55 years). With age as a continuous variable, older age was also associated with increased retention (for each additional year of age aOR 1.03 [95% CI 1.03-1.04]). Positive matching to ACDIS was associated with higher odds of retention (aOR 1.57 [95% CI 1.32-1.87]).

In further analysis with the 930 individuals matched to ACDIS, education level, household wealth, and distance from nearest clinic were not significantly associated with retention in univariable analysis. The results of multivariable analysis are displayed in Table 2. Male sex, higher initial CD4 cell count, out-migration, full-time employment, and household size of greater than ten members were all associated with lower likelihood of retention in care. With reference to age 16-25 years, older age (26-35 years, 36-45 years, and 46-55 years) was associated with increased retention; with age as a continuous variable, older age was also significantly associated with retention (for each additional year of age, aOR 1.03 [95% CI 1.02-1.05]). In-migration was also associated with increased retention.

In analyses stratified by sex, the associations with age, CD4 count, out-migration, employment, and household size remained significant for females. For males, the associations with CD4 count, employment and out-migration were similar, although only the relationship with out-migration retained statistical significance due to smaller numbers, and non-residency became significantly associated with lower retention (Table 3).

Outcomes for people lost to follow-up

432 of the 930 (46.5%) individuals matched to ACDIS did not return within 13 months for CD4 testing (compared to 58.9% for the unmatched group, $P<0.001$). Of these, 21 (4.9%) were reported to have died within the 13 month period and 72 (16.7%) migrated out of the demographic surveillance area. The remaining 339 individuals (78.5%) were documented to be alive and still a member of the

demographic surveillance system at the end of the 13 month period following their initial CD4 cell count.

Discussion

Retention in long-term HIV care both before and after the initiation of ART is important not only to reduce individual HIV-related mortality and morbidity but also as a means to deliver 'positive prevention' interventions aimed at reducing ongoing transmission. It is of major concern, therefore, that in this large primary health care HIV programme under the existing model of care for individuals not yet eligible for ART, fewer than 50% returned within 13 months for repeat CD4 cell count.

Retention in care after the initiation of ART has been the focus of much published work from sub-Saharan Africa and is seen as a key indicator of programme performance[25]. Conversely, there has only been one small study focused specifically on retention in HIV care prior to eligibility for ART, which reported retention of only 31% at twelve months in an urban South African programme[26]. Pre-ART monitoring strategies using CD4 counts have been shown in mathematical models to maximise the benefit of HIV treatment programmes and to be cost-effective in a South African setting[27,28]. However, the rates of retention reported here are much less than assumed in these models and should prompt their re-evaluation.

One plausible explanation for poor retention would be the lack of incentive for asymptomatic individuals to return for monitoring and previous work from our group has suggested that the majority return to care at the time of symptoms[29]. The package of care for individuals not yet eligible for ART has been limited in this setting, with co-trimoxazole only for those with late symptomatic disease and until now no routine implementation of isoniazid preventive therapy (IPT). This is likely to have limited the effectiveness of programmes as individuals will often return to care with opportunistic infections, possibly requiring hospitalisation, and ART will continue to be initiated late with consequent sustained high mortality rates[30]. Consistent with this we have reported no significant

change in the median CD4 count at ART initiation nor a reduction in the high early mortality rates in the first four years of the programme[13].

Recently updated national guidelines in South Africa recommend that individuals not yet eligible for ART are transferred to a 'wellness programme' for regular follow-up and repeat clinical assessment 6-monthly[31]. This also incorporates the provision of isoniazid preventive therapy (IPT) to individuals without evidence of TB disease[32]. The evidence base to guide the framework of wellness programmes is poor and research is urgently required to determine optimal and cost-effective models of care.

In this study, gender affected both access to care and retention in care. The proportion of males in this pre-ART population was even lower than that seen in antiretroviral treatment cohorts and likely reflects the different entry points to HIV care, with a large number of asymptomatic females enrolled in HIV care through antenatal HIV testing[33]. This might limit the generalisability of our findings to urban or work-based programmes with higher proportions of males. Male sex and full-time employment were associated with lower rates of retention and highlight the need to explore health care utilisation by men and to develop strategies to engage and retain men in HIV care, perhaps targeting work-based care[34]. Factors shown elsewhere to be important determinants of loss to follow-up after ART initiation such as economic status and distance to treatment point were not shown to be significant in this context[21,35-37]. This is perhaps explained by the relatively low cost of 6-monthly visits to the clinic compared to monthly visits on ART. The relationship between larger household size and lower likelihood of retention may relate to care commitments which hinder clinic attendance or financial constraints from broader distribution of the household income[38].

The decline in CD4 count for those retained in care was considerably greater than that from natural history research studies in South Africa; although the fact it was greater in those with higher initial CD4 counts was consistent[39,40]. This large CD4 decline (equivalent to 105 cells/μl per year) may represent bias in that those with greater CD4 decline may have been more likely to return for follow-up due to symptomatic progression. Additionally return visits may have been at the time of an intercurrent infection or other clinical episode which might itself lower the CD4 count. However,

these data support the hypothesis that retention in this setting is likely to be influenced more by symptomatic disease than by direct adherence to recommended monitoring strategies.

The contribution of mortality and migration to the high rate of loss to follow-up was relatively minor and the majority of those lost to follow-up were alive and remained resident within the area. No detailed information regarding causes of death is available for the group lost to follow-up and thus no conclusions can be drawn whether this mortality was HIV-related and how much the high burden of TB locally may have contributed[41]. The relationship with migration is a complicated one. This rural area is characterised by high rates of circular migration related to urban employment and young adults who migrate to urban areas for employment often return to the family home when unwell[42]. This would explain why retention was better for those individuals who were categorised as non-resident at the time of first test but became resident and the opposite relationship that those who became non-resident were less likely to have returned.

Ongoing high HIV incidence in this area despite significant scale-up of ART highlights the urgent need for improved integration of HIV care and prevention[43,44]. Retention in long-term HIV care is important to enable the delivery of targeted biomedical and behavioural interventions aimed at reduction of onward transmission[14,15]. It is of concern, therefore, that retention was particularly poor for younger people with higher CD4 counts, those who may be responsible for a significant proportion of transmission[45,46]. Whilst there has been much recent interest in the concept of universal ART as prevention[47], the evidence to support this will likely take several years to accumulate[48], and it is imperative now that integrated care and prevention programmes are prioritised and adequately resourced.

The main limitation of our study is that it is based on retrospective analysis of CD4 cell count data. There is emerging evidence that the loss to follow-up is considerable even between CD4 testing and collection of results[49]. We were unable to quantify this and our data should be interpreted as overall retention from the time of CD4 testing. Also we were unable to account for tests performed elsewhere and thus might have underestimate true retention. The proportion linked to the demographic

surveillance platform (22%) was relatively low. Of those who initially attended one of the six clinics situated within the demographic surveillance area, 46% were successfully linked. Whilst mobility of patients within the sub-district and drawing in of patients from outside the sub-district might partly explain this, it is also possible that incomplete patient identifiers hampered the linkage process. The linked group had better retention than the unlinked individuals, which might partly reflect the fact that the demographic surveillance area is less rural and more developed and there is greater access to services than the rest of the sub-district.

In conclusion, we have demonstrated that under existing models of public sector HIV care retention prior to eligibility for ART is poor, particularly for younger individuals with higher initial CD4 cell count. The next phase of HIV counselling and testing scale-up is likely to significantly increase the number of diagnosed HIV-infected individuals in care but not yet in need of ART[50]. Trials to evaluate different models of pre-ART care or wellness programmes, both facility-based and community-based, are an urgent priority. If the substantial benefits of the massive scale-up of HIV treatment and care programmes are to be maintained then we need to build an evidence base with which to inform the design of programmes to offer comprehensive care throughout the continuum of HIV infection.

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Table 1. Baseline characteristics of included individuals (*n*=4,223)

Variable		Matched individuals (*n*=930)	Unmatched individuals (*n*=3,293)	*P*-Value
Sex, % male (95% CI)		16.6 (15.4-17.9)	14.2 (12.0-16.5)	0.075
Age, yrs, median (IQR)		32 (26-41)	30 (24-38)	<0.001
CD4 count, cells/µl, median (IQR)		396 (297-546)	399 (297-556)	0.710
Residency status	Always resident	533 (57.3%)		
	Always non-resident	245 (26.3%)		
	Partly in-migrant	41 (4.4%)		
	Partly out-migrant	111 (11.9%)		
Employment	Unemployed	474 (51.0%)		
	Part-time	47 (5.1%)		
	Full-time	199 (21.4%)		
	Missing data	210 (22.6%)		
Education level	None	81 (8.7%)		
	Primary	175 (18.8%)		
	Secondary	413 (44.4%)		
	Missing data	261 (28.1%)		
Household size	1-5	151 (16.2%)		
	6-10	286 (30.8%)		
	>10	236 (25.4%)		
	Missing data	257 (27.6%)		

CI, confidence interval; IQR, interquartile range

Table 2. Logistic regression of factors associated with retention in care for matched individuals (*n*=930)

Variable*		*n*	uOR	95% CI	aOR	95% CI	*P*-Value
Sex	Female	797	1		1		
	Male	133	1.06	0.74-1.54	0.71	0.53-0.95	0.022
Age, years	16-25	195	1		1		
	26-35	371	1.49	1.05-2.12	1.34	1.10-1.65	0.005
	36-45	221	2.70	1.82-4.02	2.32	1.63-3.30	<0.001
	46-55	121	3.62	2.23-5.87	2.82	1.88-4.21	<0.001
	>55	22	1.84	0.76-4.46	1.91	0.64-5.71	0.246
Initial CD4 count, cells/µl	201-350	347	1		1		
	351-500	308	0.65	0.47-0.89	0.71	0.55-0.90	0.005
	>500	275	0.45	0.33-0.62	0.47	0.32-0.68	<0.001
Residency status	Resident	533	1		1		
	Non-resident	245	0.77	0.54-1.00	0.93	0.59-1.48	0.767
	In-migrant	41	1.77	0.88-3.54	2.31	1.22-4.38	0.010
	Out-migrant	111	0.38	0.25-0.58	0.40	0.22-0.72	0.002
Employment	Unemployed	474	1		1		
	Part-time	47	1.88	0.98-3.59	1.36	0.86-2.16	0.187
	Full-time	199	0.77	0.55-1.08	0.68	0.47-0.98	0.036
Household size	1-5	151	1		1		
	6-10	286	0.98	0.66-1.46	0.98	0.67-1.44	0.921
	>10	236	0.53	0.35-0.81	0.59	0.40-0.89	0.011

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval

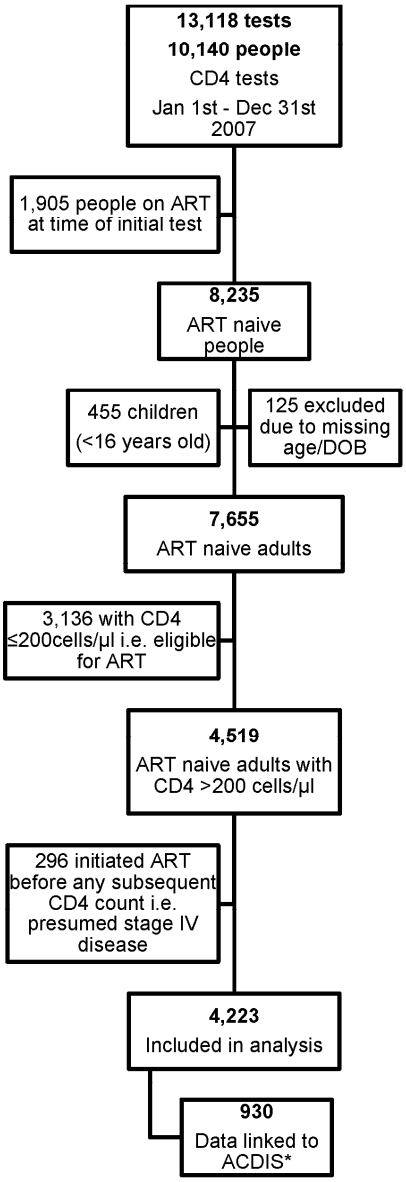
*Education, asset wealth index, and distance to nearest clinic were not significant in univariable analysis and were not included in the multivariable model. The effect of missing data was not significant for any variable (not shown)

Table 3. Multivariable analysis of factors associated with retention in care, by sex

Variable		FEMALES (*n*=797)			MALES (*n*=133)		
		aOR	**95% CI**	***P*-Value**	**aOR**	**95% CI**	***P*-Value**
Age, years	16-25	1			1		
	26-35	1.33	1.07-1.64	0.009	1.12	0.34-3.57	0.863
	36-45	2.52	1.74-3.64	<0.001	1.33	0.38-4.71	0.655
	46-55	3.10	1.79-5.36	<0.001	1.69	0.38-7.48	0.492
	>55	2.16	0.50-9.31	0.303	0.89	0.08-9.82	0.926
Initial CD4 count, cells/µl	201-350	1			1		
	351-500	0.68	0.55-0.83	<0.001	0.90	0.49-1.65	0.733
	>500	0.46	0.32-0.66	<0.001	0.55	0.26-1.15	0.112
Residency status	Resident	1			1		
	Non-resident	1.19	0.66-2.18	0.561	0.21	0.11-0.39	<0.001
	In-migrant	2.01	0.85-4.76	0.111	2.12	0.59-7.65	0.250
	Out-migrant	0.42	0.22-0.81	0.010	0.23	0.07-0.79	0.020
Employment	Unemployed	1			1		
	Part-time	1.66	0.84-3.30	0.147	0.66	0.23-1.91	0.447
	Full-time	0.64	0.44-0.93	0.018	0.88	0.41-1.86	0.730
Household size	1-5	1			1		
	6-10	0.99	0.71-1.38	0.939	1.03	0.33-3.23	0.948
	>10	0.57	0.39-0.85	0.005	0.95	0.23-3.88	0.943

aOR, adjusted odds ratio; CI, confidence interval

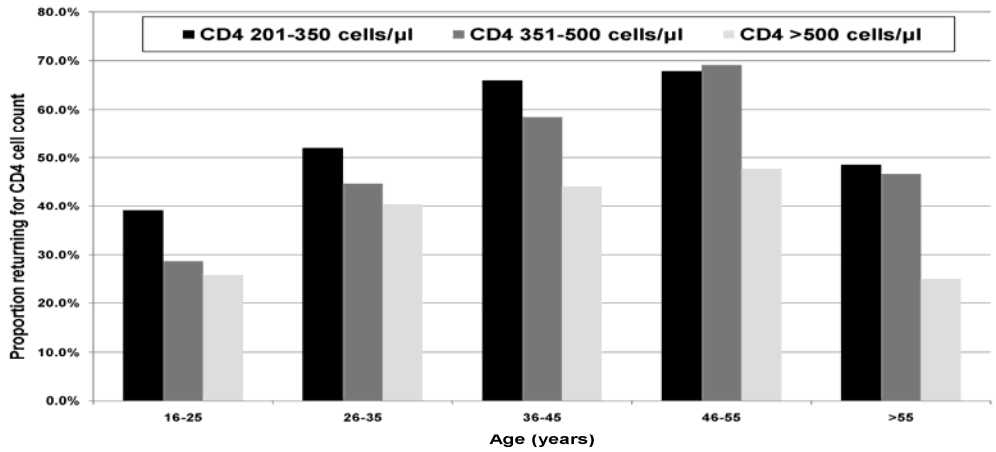
Figure 1. Inclusion of individuals in analyses



*Africa Centre Demographic Information System

Figure 2. Retention stratified by age and initial CD4 cell count. A, Females. B, Males.

A.



B.